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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,463	GUILLEMETTE, CHANTAL	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/16/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8-11,13-15,18-31,33 and 34* is/are pending in the application.

4a) Of the above claim(s) *18-29 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 8-15, 30, and 33-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/16/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed April 16, 2008. This action is FINAL.

Claims 1, 8-11, 13-15, 18-31, and 33-34 are currently pending. Claims 1, 15, and 31 have been amended. Claims 33-34 are newly presented. Claims 18-29 and 31 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Accordingly Claims 1-2, 8-11, 13-15, and 30 will be discussed herein.

Interview

2. The interview record is complete.

Withdrawn Objections

3. The objection made to claim 1 in section 3 of the Office Action of January 17, 2008 is withdrawn in view of amendment made to the claim.

Withdrawn Rejections

4. The declaration submitted under 37 CFR 1.132 filed April 16, 2008 is sufficient to overcome the rejection of claims 1, 8-11, 13-15, and 30 based upon enablement. Specifically the declaration provides evidence that the association found between the T-275A substitution and higher glucuronidation is statistically significant.

Specification

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) on the attached Notice To Comply and reiterated below.

In the instant case Figure 20 contains amino acid sequences that are not listed in the Sequence Listing. Patent Applications which contain disclosures of sequences must contain, as a separate part of the disclosure, a paper copy disclosing the sequences, referred to as the "Sequence Listing". Applicants are also required to file a computer readable form (CRF) copy of the "Sequence Listing". Additionally a statement that the content of the paper and computer readable forms are the same must be submitted. For further guidance see MPEP 2422. Further it is noted that where the description of a patent application discuss a sequence that is set forth in the "Sequence Listing", reference must be made to the sequence by use of a sequence identifier, preceded by "SEQ ID NO:" in the text of the description even if the sequence is also embedded in the text. Therefore Applicants are required to identify each amino acid sequence in Fig 20 by its SEQ ID NO: in either the brief description of the drawings or the drawings themselves.

Further the specification (page 25, lines 15) appears to have a typo. Specifically "UGTA9" should be UGT1A9". Also for consistency the title of Example V should be

changed to "Effect of the expression of UGT1A9 proteins on glucuronidation by liver microsomes" to avoid confusion.

Since this objection is being presented in a FINAL Office Action for the first time, an amendment submitted after final to correct this defect would be entered after final.

Drawings

6. Figure 13a is objected to because the title of the graph is "SN-38 G formation (nmoles/mg/min) by UGT1A1 protein level", however the brief description Fig 13a states that it illustrates the correlation between the UGT1A9 protein expression and glucuronidation activity. Further the specification (page 25) teaches that Figure 13a shows a positive correlation between glucuronidation of SN-38 and protein level of UGT1A9. Thus it appears that the title of the graph in Fig 13a has been mislabeled. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application

must be labeled in the top margin as either “Replacement Sheet” or “New Sheet” pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Since this objection is being presented in a FINAL Office Action for the first time, an amendment submitted after final to correct this defect would be entered after final.

Claim Rejections - 35 USC § 112 2nd paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 8-11, 13-15, 30, and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 8-11, 13-15 and 30 are rejected as being indefinite in that the goal of the method and the final step do not agree. The claims are drawn to "a method for screening human individuals for variations in UGT1A9 metabolism”. However, the claims recite the final step of determining the presence of a T-275A substitution, whereby the presence of the substitution is indicative of increased UGT1A9 glucuronidation activity. The claims do not result in the screening of human individuals for ANY variation in UGT1A9 metabolism since only a specific variation (T-275A) is being screened for which is indicative of increased UGT1A9 glucuronidation activity. This rejection could be overcome by amending the preamble to recite "A method for

screening a human individual for increased UGT1A9 glucuronidation activity of a compound that is metabolized through UGT1A9 glucuronidation".

Claim 1 recites the limitation "said individual" in line 5. There is insufficient antecedent basis for this limitation in the claim. The method is drawn to screening human individuals (plural), however the method only requires obtaining a single nucleic acid sample from said individual.

Claim 1 recites the limitation "said nucleotide sequence of UGT1A9" in lines 6 and 8. There is insufficient antecedent basis for this limitation in the claim because the claim does not refer to a “nucleotide sequence”.

Claims 13-15 and 34 are rejected as being indefinite in that the goal of the method and the final step do not agree. Claim 34 is drawn to "a method for screening human individuals for variations in glucuronidation activity”. However, the claims recite the final step of determining the presence of a T-275A substitution. The steps listed in the method do not result in screening a human individual for variations in glucuronidation activity. Therefore, it is unclear as to whether the claims are intended to be limited to methods for screening a human individual for variations in glucuronidation activity or methods for determining the presence of a T-275A substitution.

Claims 13-15 and 33 are indefinite because claim 33 is drawn to a method for detecting polymorphisms (plural) in a UGT1A9 promoter; however the method only requires determining the presence of a single T-275A polymorphism.

Claim Rejections - 35 USC § 112 1st paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 13-15 and 33-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

In the instant case the specification does not appear to provide support for the amendment which recites "wherein the presence of said T-275A substitution correlates with increased expression of the UGT1A9 gene". This phrase encompasses a method wherein the presence of the T-275A substation correlates with increased mRNA **and/or** protein expression of UGT1A9 in ANY tissue type. The specification does not provide data showing that the T-275A mutation is directly associated with increased UGT1A9 protein levels (data is only provided for the 3 other SNPs), however the specification asserts that presence of the T-275A substitution correlates with increased glucuronidation activity and that increased glucuronidation activity is associated with increased protein levels of UGT1A9 in liver microsomes. Additionally the Applicants 132 declaration filed April 16, 2008 provides evidence to substantiate the assertion that the T-275A mutation is actually associated with an increased expression of the UGT1A9

protein in liver microsomes. Thus while the specification discloses a method wherein the presence of said T-275A substitution correlates with increased protein expression of the UGT1A9 in liver microsomes, the specification does not provide specific support for a method wherein the presence of said T-275A substitution correlates with increased expression of the UGT1A9 gene.

10. Claims 13-15 and 33-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting a polymorphism in a UGT1A9 gene promoter of a human subject, wherein the method comprises obtaining a sample of nucleic acid from the human subject and directly assaying said sample for the presence of a T-275A substitution in the UGT1A9 gene wherein the presence of said substitution correlates with increased protein expression of UGT1A9 in the liver as compared to an individual without the substitution, does not reasonably provide enablement for detecting polymorphisms in a UGT1A9 gene promoter of a human subject wherein the method comprises determining the presence of a T-275A substitution in said promoter wherein the presence of said T-275A substitution correlates with increased expression of the gene. Further while being enabling for screening human individuals for variation in glucuronidation activity, wherein the method comprises obtaining a sample of nucleic acid from the human subject and directly assaying said sample for the presence of a T-275A substitution in the UGT1A9 gene wherein the presence of said substitution correlates with increased protein expression of UGT1A9 in liver compared to an individual without the substitution, does not

reasonably provide enablement for screening human individuals for variation in glucuronidation activity wherein the method comprises determining the presence of a T-275A substitution in said promoter wherein the presence of said T-275A substitution correlates with increased expression of the gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Nature of the Invention

Claim 33 is drawn to a method for detecting polymorphisms in a UGT1A9 gene promoter of a human subject. The claim comprises determining the presence of a T-275A substitution in said promoter wherein the presence of said T-275A substitution correlates with increased expression of the gene. Claim 34 is drawn to a method for screening human individuals for variation in glucuronidation activity. The method comprises determining the presence of a T-275A substitution in said promoter, wherein the presence of said T-275A substitution correlated with increased expression of the UGT1A9 gene. The invention is in a class of inventions which the CAFC has

characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Scope of the Claims:

In the instant case claims 33-34 do not recite how the T-275A substitution is being detected. There are no active process steps such as obtaining a sample and assaying the sample for the presence of the T-275A substitution. Therefore the claims encompass any means of determining the presence of a T-275A substitution, including nucleic acid analysis and/or amino acid analysis. The claims also recite the phrase "wherein the presence of said T-275A substitution correlates with increased expression of the UGT1A9 gene". Thus the claims encompass a method wherein the presence of the T-275A substation correlates with increased mRNA **and/or** protein expression of UGT1A9. This phrase is also problematic because the claims do not set forth what the "increased expression" is relative to. For example the increased expression could be relative to an individual with the T allele at position -275 or some other unspecified individual. Further the claims encompass a method wherein the increased expression is present in any tissue type (liver, kidney, blood etc).

Teachings in the Specification and Examples:

The specification (page 1) teaches that the UDP-glucuronosyltransferase enzymes are a set of enzymes that increase the polarity of xenobiotics, drugs, and endogenous compounds to facilitate their excretion from the body. Any perturbation in the glucuronidation pathway has the potential to modify the elimination, the detoxification or the pharmacokinetic parameters of a given drug, and consequently

drug clearance. As a result, in situations where the activity of the glucuronidation pathway is reduced it is to be expected that changes in the biological activity, sometimes toxicity, of the compounds will ensue. Therefore human genetic variations leading to differences glucuronidation rates could influence the activity of drugs and other chemicals.

The specification (example 3) states that the primary objective of this study was to examine the genomic sequences of the UGT1A9 gene promoter sequence to identify novel expression polymorphisms and to determine whether or not these polymorphic variations would affect the expression of the UGT1A9 protein. Ten novel polymorphic variations were identified in the UGT1A9 promoter, including a variation that causes a T to A substitution at position -275 of the UGT1A9 gene. The specification further teaches that three of the novel polymorphic variations in the UGT1A9 promoter (at positions -2152, -665, and -440) were associated with higher expression of UGT1A9 proteins in liver microsomes (See Fig 8a-8e).

Further the specification (example 4) states that once it was established that polymorphic variations in the promoter region of the UGT1A9 gene can modulate expression of the UGT1A9 protein, it was interesting to study the impact of these mutations on glucuronidation by human liver microsomes. Specifically Fig 12 shows a positive correlation between the presence of the -275 mutated alleles and higher glucuronidation rate.

Additionally the specification (example 5) states that the Applicants also attempted to determine if an association between the expression of the UGT1A9 protein

and glucuronidation formation could exist. Figure 13a demonstrates that there is a positive correlation between glucuronidation of SN-38 and protein level of UGT1A9. Figure 13b demonstrates that there is a positive correlation between glucuronidation of MPA and protein level of UGT1A9.

For the record is it noted that the specification does not provide data showing that the -275 mutation is directly associated with increased UGT1A9 protein levels (data is only provided for the 3 other SNPs), however the specification asserts that presence of the T-275A substitution correlates with increased glucuronidation activity and that increased glucuronidation activity is associated with increased protein levels of UGT1A9. However the Applicants 132 declaration filed April 16, 2008 provides evidence to substantiate the assertion that the T-275A mutation is actually associated with an increased expression of the UGT1A9 protein in liver microsomes. It is also noted that the Applicants claims are broader than the scope of enablement. For example the specification does not teach that the T-275A substitution was associated with higher mRNA expression of UGT1A9 which is also encompassed by the claims. Further the specification only teaches that the patients carrying the mutation have increased protein expression relative to patients who do not carry the mutation. Additionally the specification does not teach that T-275A substitution was associated with higher protein expression of UGT1A9 in any type of tissue (liver, kidney, Blood), since only liver tissues were tested.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The claims recite that the presence of the T-275A substitution correlates with

increased expression of the UGT1A9 gene. Thus the claims encompass methods wherein the presence of the T-275A substitution correlates with increased mRNA expression of UGT1A9 AND increased protein expression of UGT1A9. In the instant case the specification only teaches that the T-275 substitution was found to be associated with increased protein expression of UGT1A9. In the instant case it is relevant to point out the unpredictability as to whether or not a measure of mRNA expression is equivalent to a measure of protein expression. Chan (Genomics and Proteomics) teaches that cells have elaborate regulatory mechanisms at the level of transcription, post-transcription, and post-translation (p.1, last paragraph), and that transcript and protein abundance measurements may not be concordant (p.3, sixth full paragraph). Thus even though the specification has taught that the presence of the T-275T substitution is associated with increased UGT1A9 protein levels, it is unpredictable as to whether or not the T-275A substitution would also be associated with increased mRNA levels.

Further, it is unpredictable as to whether the results obtained in liver tissues could be extrapolated to other tissue types. Knowledge that the T-275A substitution is associated with increased protein levels of UGT1A9 in liver microsomes does not allow one to conclude that this mutation will also be associated with increased protein levels of UGT1A9 in other tissue types. The specification does not teach any other tissue types that normally express the UGT1A9 protein. According to Gene Card for UGT1A9 (http://www.genecards.org/cgi-bin/carddisp.pl?gene=UGT1A9&search=ugt1a9), the UGT1A9 is primarily expressed in the liver and kidney but also is expressed in low

levels in the thymus, lungs, skeletal muscles etc. Further the specification (page 24) teaches that UGT1A9 protein expression is highly variable. Thus in the absence of information it is highly unpredictable as to whether the T-275A substitution is associated with increased protein levels of UGT1A9 in other tissue types.

Amount of Direction or Guidance Provided by the Specification

The claims state that the T–275A substitution of the UGT1A9 gene is associated with increased expression of the UGT1A9 gene, which encompasses increased mRNA expression of the UGT1A9 gene as well as increased protein expression of UGT1A9. In the instant case there is no association study between the phenotype (increased mRNA expression of UGT1A9) and the recited genotype (T-275A substitution) described in the specification. This absence is significant in such a highly unpredictable art. Therefore to determine if an association actually exists between this mutation and increased mRNA expression would require extensive experimentation. For example, such experimentation may involve sequencing the UGT1A9 gene of a large number of individuals and performing nucleic acid analysis to determining mRNA expression. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he

scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification only teaches an association between the T-275A substitution and increased protein expression of UGT1A9 in liver microsomes. The specification is silent with regard to an association between the T-275A substitution and increased mRNA expression of UGT1A9. Further the specification is silent with regard to an association between the T-275A substitution and increased expression of UGT1A9 in other tissue types. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
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/Carla Myers/
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